International Journal of Research in Medical Sciences
Ahmad N et al. Int J Res Med Sci. 2017 Oct;5(10):4595-4599
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20174603

Original Research Article

Clinical and etiological profile of unprovoked thrombosis in young patients admitted at a tertiary care hospital

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Received: 13 August 2017
Accepted: 07 September 2017

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ABSTRACT

Background: It is now possible to identify acquired and hereditary risk factors in a substantial percentage of patients presenting with a venous thrombotic event. The objective of the study was to study the clinical and etiological profile of patients with unprovoked thrombosis in young patients.
Methods: Twenty-one patients 09 males (42.8%) and 12 females (57.14%) with a mean age of 29.67±5.21 were studied, who presented with unprovoked thrombosis.
Results: Among 21 patients studied most common presentation was deep venous thrombosis of lower limbs (38.09%) followed by recurrent abortions with deep venous thrombosis (14.28%) and cerebellar infarction (14.28%). In etiological profile, the most common thrombophilla was factor V Leiden mutation (28.57%) followed by antiphospholipid antibody syndrome (23.8%), protein C deficiency (19.04%), methylene tetrahydrofolate reductase (9.52%) and antithrombin, prothrombin gene mutation, hyperhomocystenemia and janus kinase 2 mutations (4.76%). Among 6 patients of factor V Leiden mutation 3 presented with deep venous thrombosis of lower limbs, 1 patient each with middle cerebral artery infarct, juglar vein thrombosis and subclavian vein thrombosis respectively.
Conclusions: Factor V Leiden mutation is the most common inherited thrombophillias which has been "substantiated from various studies.

Keywords: Deep venous thrombosis, Factor V Leiden, Thrombophilias, Thromboembolism, Warfarin

INTRODUCTION

Thrombophilia refers to any persistent hypercoagulable state that is associated with increased risk of thromboembolism. It may be genetically determined, acquired, or both.[1] Thrombophilia, which involves interactions between inherited and acquired risk factors, has been suggested as a possible cause of recurrent spontaneous abortions.[2] The most common types of hereditary thrombophilia are factor V leiden (FVL), prothrombin (PTH), and methylenetetrahydrofolate reductase (MTHFR) genes mutations, but these are usually undiagnosed because most carriers are asymptomatic.[3]

Thrombophilias are a group of inherited conditions associated with an increased risk of developing venous thromboembolism(VTE).[4] A point mutation of factor V (G1691A) known as factor V Leiden (FVL), the most frequent of the thrombophilias, has an approximate incidence of 5% in the Caucasian population. FVL may be detected by deoxyribonucleic acid (DNA) analysis.[5]

The functional consequence of the mutation is an impaired inactivation of factor V, resulting in increased thrombin generation. The second most frequent thrombophilia is a single nucleotide substitution in the prothrombin (Factor II) molecule promoter region (G20210A), a condition also detected by DNA analysis. The point mutation functionally increases the concentration of prothrombin. In their heterozygous forms, FVL or G20210A are associated with a modest increase in VTE risk. Rare homozygous or compound heterozygous individuals have a greater VTE risk.[6] If an individual with VTE has FVL, G20210A or both, appropriate counseling should be provided, including careful evaluation of the duration of VTE treatment, need for family screening and interventions to minimize future VTE risk.[7]

Currently recommended indications for thrombophilia testing include idiopathic or recurrent venous thromboembolism; a first episode of venous thromboembolism at a "young" age (e.g., < 40 years); a family history of venous thromboembolism (in particular, a first-degree relative with thrombosis at a young age); venous thrombosis in an unusual vascular territory (e.g., cerebral, hepatic, mesenteric, or renal vein thrombosis); and neonatal purpura fulminans or warfarin-induced skin necrosis. When two or more of these thrombosis characteristics are present, the prevalence of antithrombin, protein C or protein S deficiency as well as the factor V Leiden and prothrombin G20210A mutations are increased. Consequently, a "complete" laboratory investigation is recommended for patients who meet these criteria, while more selective (e.g., activated protein C resistance/factor V Leiden, prothrombin G20210A mutation) is recommended for other patients.[4] VTE susceptibility genes are present in 5-10% of the general population and in at least 40% of patients with VTE. An association with VTE has been firmly established for antithrombin (AT), protein C (PC), and protein S (PS) deficiencies, as well as for factor V Leiden (FVL) and prothrombin (PT) 20210A.[8] The aim of this study was to study the clinical presentation and etiological profile of patients with unprovoked thrombosis.

METHODS

This study was conducted in department of internal medicine Government Medical College Srinagar. The study included 21 patients aged between 20-40 years with unprovoked thrombosis. A proper informed consent was taken from all patients included in the study. All other patients with provoked and postpartum thrombosis were excluded. From all the patients, 5ml of venous blood samples were obtained under proper aseptic conditions and were immediately placed in sterile vaccutainer tubes. The samples were sent to laboratory for thrombo check profile. As these patients presented with unprovoked thrombosis, a thrombophilic profile was sent for analysis before the start of anticoagulation. Clinical presentaion and etiological profiles of the patients were noted and correlated.

Statistical analysis

The demographic data and labarotory parameters were analysed by SPSS version 20. Qualitative variables were expressed as percentages and quantitative ones as mean ±SD.

RESULTS

Overall the study included 21 subjects, 9(42.85%) males and 12 (57.14%) females with a mean age of 29.67±5.21 years (Table 1).

Table 1: Patient characteristics.

Patient characteristic	Mean± SD
Age	29.67 ±5.21
Haemoglobin	12.6±2.45
Total leucocyte count	5.5±1.147
Platelet count	267.9±85.99
Urea	15.14±5.29
Creatinine	0.70±0.25
Bilirubin	0.92±0.31
Aspartate transaminase	29.76±7.09
Alanine transaminase	33.61±10.72
Alkaline phosphatase	88.90±19.90
Albumin	3.83±0.33

Data is expressed as mean±SD.

Table 2: Clinical presentation of the study patients.

Clinical presentation	Number of study subjects	% age
DVT lower limbs	08	38.09
Recurrent Abortions with DVT	03	14.28
Cerebellar infarct	03	14.28
MCA infarct	01	4.76
Juglar vein thrombosis	01	4.76
Mesenteric vein thrombosis	01	4.76
Axillary vein thrombosis	01	4.76
Sigmoid sinus thrombosis	01	4.76
Recurrent pleuritic chest pain	01	4.76
Subclavian vein thrombosis	01	4.76

Deep venous thrombosis was the most common presentation. DVT: Deep venous thrombosis, MCA: Middle cerebral artery.

The most common presentation among study subjects was DVT lower limbs in 08 patients (38.09%), followed by recurrent abortions with DVT in 03(14.28%), cerebellar infarct in 03 (14.28%), while as juglar vein thrombosis, mesenteric vein thrombosis, axillary vein thrombosis, sigmoid sinus thrombosis, subclavian vein thrombosis and recurrent pleuritic chest pain were present in 01 patients (4.76%) each respectively (Table 2).

Among 21 patients the most common inherited thrombophillia was factor V Leiden mutation in 6 subjects (28.57%) followed by APLA (antiphospholipid antibody) in 05 (23.8%), protein C deficiency in 04 (19.04%), MTHFR mutation in 02 (9.52%), Antithrombin III deficiency, Prothrombin gene mutation, JAK 2 (Janus kinase 2) mutation and hyperhomocystenemia in 01 (4.76%) patient each respectively (Table 3). Among 06 patients of factor V Leiden mutation, 03 (50%) presented with DVT lower limbs. Out of 5 patients with APLA, 04 (80%) presented with DVT lower limbs with recurrent abortions and 01 (20%) presented with DVT lower limbs only. Out of 03 subjects who had protein C mutation, 02 (66.67%) had cerebellar infarct and 01 (33.33%) had DVT lower limbs. Out of 02 patients with MTHFR 01 (50%) had axillary vein thrombosis and 01 (50%) had mesenteric vein thrombosis (Table 4).

Table 3: Etiological profile of the study patients.

thrombo check profile	Number of study subjects	% age
Factor V Leiden mutation	6	28.57
APLA	5	23.8
Protein C deficiency	4	19.04
Antithrombin III mutation	1	4.76
Prothrombin gene mutation	1	4.76
MTHFR mutations	2	9.52
JAK 2 mutations	1	4.76
Hyperhomocystinemia	1	4.76

Factor V leiden mutation was the most common etiology of unprovoked thrombosis among study patients. APLA: Antiphospholipid antibody, MTHFR: methylene tetrahydrofolate reductase, JAK 2: Janus kinase 2.

Table 4: Correlation between etiological profile and clinical presentation.

	DVT lower limbs	DVT with abortions	Cerebellar infarct	MCA infarct	Juglar vein thrombosis	Axillary vein thrombosis	Mesenteric vein thrombosis	Subclavian thrombosis	Sigmoid Sinus Thrombosis	Chest pain
Factor v Leiden mutation	03	-	-	01	01	-	-	01	-	-
APLA	01	04	-	-	-	-	-	-	-	-
Protein C deficiency	01	-	02	-	-	-	-	-	-	01
MTHFR mutations	-	-	-	-	-	01	01	-	-	-
Antithrombin III mutation	-	-	-	-	-	-	-	-	01	-
Prothrombin gene mutations	01	-	-	-	-	-	-	-	-	-
JAK 2 mutations	-	-	01	-	-	-	-	-	-	-
Hyperhomocystinemia	-	-	-	01	-	-	-	-	-	-

DISCUSSION

Venous thromboembolism (VTE) occurs for the first time in ≈ 100 persons per 100,000 each year in the United States. Approximately one third of patients with symptomatic VTE manifest pulmonary embolism (PE), whereas two thirds manifest deep vein thrombosis (DVT) alone.[9]

The most common cause of inherited thrombophilla is factor V Leiden mutations. Genetic variants leading to a persistent hypercoagulable state may predispose to thrombotic events. A recently discovered G to A mutation at position 1691 of the factor V gene (factor V Leiden mutation), occurring in 3% to 5% of the normal Caucasian population, has emerged as a major genetic risk factor of venous thrombosis.[10] The role of this mutation for arterial vascular events, in particular cerebrovascular disease, is still under discussion.[11-15]

Factor V Leiden is an autosomal dominant genetic condition that exhibits incomplete penetrance, i.e. not every person who has the mutation develops the disease. The condition results in a factor V variant that cannot be as easily degraded by aPC (activated Protein C). The gene that codes the protein is referred to as F5. Mutation of this gene-a single nucleotide polymorphism (SNP) is located in exon 10[4].People with factor V Leiden thrombophilia have a higher than average risk of developing deep venous thrombosis . Factor V Leiden thrombophilia also increases the risk that clots will break away from their original site and travel through the bloodstream. These clots can lodge in the lungs, where they are known as pulmonary emboli. Although factor V Leiden thrombophilia increases the risk of blood clots, only about 10 percent of individuals with the factor V Leiden mutation ever develop abnormal clots.[16] In present study most of the patients had factor V Leiden mutation, which was the most common inherited thrombophilia (28.57%) and 50% of patients with this mutation presented with DVT lower limbs.

Antiphospholipid syndrome is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies. Antiphospholipid antibody provokes blood clots (thrombosis) in both arteries and veins as well as pregnancy related complications such as miscarriage, stillbirth, preterm delivery, and severe pre-eclampsia. The diagnostic criteria require one clinical event, i.e.

thrombosis or pregnancy complication, and two antibody blood tests spaced at least three months apart that confirm the presence of either lupus anticoagulant, or anti-β_2-glycoprotein-I.[17] Antiphospholipid syndrome can be primary or secondary. Primary antiphospholipid syndrome occurs in the absence of any other related disease. Secondary antiphospholipid syndrome occurs with other autoimmune diseases, such as systemic lupus erythematosus (SLE). In rare cases, APS leads to rapid organ failure due to generalised thrombosis; this is termed "catastrophic antiphospholipid syndrome" (CAPS or Asherson syndrome) and is associated with a high risk of death.[18] In our study APLA was the second most common thrombophilia (23.8%) and 80% patients presented with DVT lower limbs with recurrent abortion and 20% with DVT lower limbs only.

Protein C deficiency is associated with an increased incidence of venous thromboembolism , whereas no association with arterial thrombotic disease has been found.[19] The main function of protein C is its anticoagulant property as an inhibitor of coagulation factors V and VIII. A deficiency results in a loss of the normal cleaving of factors Va and VIIIa. There are two main types of protein C mutations that lead to protein C deficiency.[20]

Type I

Quantitative defects of protein C (low production or short protein half-life).

Type II

Qualitative defects, in which interaction with other molecules is abnormal. Defects in interaction with thrombomodulin, phospholipids, factors V/VIII and others have been described.

The majority of people with protein C deficiency lack only one copy of the functioning genes, and are therefore heterozygous. Before 1999, only sixteen cases of homozygous protein C deficiency had been described.[19] In this study 19.04% patients had protein C deficiency out of which 25 % presented with DVT lower limbs,50% with cerebellar infarct and 25% with pulmonary thromboembolism.

CONCLUSION

In this study conducted over a period of 3 years in the department of internal medicine at GMC Srinagar, the most common cause for unprovoked thrombosis was found to be factor V Leiden mutation. Small sample size was limitation of this study. Large multicenter trials are required to correlate the findings of our study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ahmad N, Akhter N, Sheikh TA. Clinical and etiological profile of unprovoked thrombosis in young patients admitted at a tertiary care hospital. Int J Res Med Sci 2017;5:4595-9.